

**BIOCHEMICAL EFFECTS OF LOW-FLOW ANESTHESIA WITH INHALATION AGENTS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERY****BIOHEMIJSKI EFEKTI ANESTEZIJE NISKOG PROTOKA INHALACIJSKIM AGENSIMA KOD PACIJENATA PODVRGNUTIH LAPAROSKOPSKOJ HIRURGIJI***Remziye Sivaci, Serap Demir, Tulay Koken, Yasar Sivaci, Sezgin Yilmaz**Afyon Kocatepe University, School of Medicine and Pulmonary Hospital, Afyon, Turkey*

**Summary:** This study was designed to investigate the effects of low-flow anesthesia with sevoflurane and desflurane on renal and hepatic functions in patients undergoing laparoscopic abdominal surgery. Twenty patients with ASA I or II (American Society of Anesthesiologists classification) physical scores were included in the study. There were no significant differences between sevoflurane and desflurane groups with respect to age, weight, body mass index, duration of the operation and the anesthesia. In both groups, renal function parameters such as urea, BUN, creatinine and calculated creatinine clearance did not show significant differences at 24 and 48 hours. Homocysteine levels, which showed renal metabolic function, did not change significantly at 24 and 48 hours when compared to baseline levels in both groups. Transaminases were not significantly different between the two groups from baseline to 24 and 48 hours. These differences between the preoperative and postoperative values of biochemical parameters were similar for both anesthetic groups ( $p > 0.05$ ). Low-flow anesthesia did not cause impairment in terms of renal and hepatic functions.

**Keywords:** biochemical parameters, homocysteine, free radicals, volatile anesthetics, low-flow anesthesia

**Introduction**

A wide range of intraabdominal surgical procedures are increasingly being performed laparoscopically (1). In laparoscopic surgery patients, fresh gas flow rates and the kind of anesthetic agents used are

**Kratak sadržaj:** Ova studija je osmišljena kako bi se ispitalo uticaj anestezije niskog protoka sevofluranom i desfluranom na funkcije bubrega i jetre kod pacijenata podvrnutih laparoskopskoj hirurgiji. Studijom je obuhvaćeno dvadeset pacijenata sa fizičkim skorom I ili II određenim na osnovu klasifikacije Američkog društva anesteziologa. U pogledu uzrasta, težine, indeksa telesne mase, trajanja operacije i anestezije nije bilo značajnih razlika između grupa kod kojih su primenjeni sevofluran i desfluran. U obe grupe parametri bubrežne funkcije kao što su urea, BUN, kreatinin i izračunati klirens kreatinina nisu pokazali značajne razlike posle 24, odnosno 48 sati. Nivoi homocisteina, koji odražavaju bubrežnu metaboličku funkciju, nisu se značajno promenili posle 24, odnosno 48 sati, u poređenju sa početnim nivoima u obe grupe. Transaminaze se kod obe grupe nisu značajno razlikovale od početnih vrednosti kao ni posle 24 i 48 sati. Ove razlike u vrednostima biohemijskih parametara pre i posle operacije bile su slične u obe anestezirane grupe ( $p < 0,05$ ). Anestezija niskog protoka nije izazvala oštećenja bubrežne kao ni hepatičke funkcije.

**Ključne reči:** biohemijski parametri, homocistein, slobodni radikali, isparljivi anestetici, anestezija niskog protoka

important from the point of view that they have different effects on the organ systems. Differences emerge from the blood/gas and tissue/blood solubility coefficients of these drugs (2). Therefore, low-flow anesthesia is mostly preferred because it has the advantages of less anesthetic consumption, decreased atmospheric pollution and reduced cost in laparoscopic surgery. Especially, new volatile agents such as sevoflurane or desflurane are being used (3). In previous clinical studies no adverse effects of sevoflurane anesthesia were shown at various rates of fresh gas flow in normal renal function (4). *In vivo* and *in vitro* degradation of sevoflurane produces inorganic fluoride and vinyl ether (Compound A), which has the

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potential to harm renal and hepatic function. In rats, it was shown that both degradation products from 150 to 300-ppm/h concentrations could injure rat kidneys and compound A (CpA) caused corticomedullary tubular necrosis localized to the proximal tubule (5). However, its effect on the human kidney is not known (6). The few studies of the renal effects of sevoflurane given with fresh gas flows of  $\leq 2$  L/min have not demonstrated nephrotoxicity. But, such studies usually assess renal function by changes in serum creatinine or blood urea nitrogen (BUN) (2). In a previous study, it was indicated that the fluoride resulting from sevoflurane anesthesia at a higher fresh gas inflow rate (normal range: 2–6 liter/min) did not produce renal injury in humans (7). Kharasch et al. (8) compared the effects of long duration ( $9.2 \pm 3.6$  MAC hours) low-flow sevoflurane anesthesia (LFSA) and isoflurane anesthesia on renal and hepatic functions. They reported that CpA of volatile agents had no significant effect on renal function unless it was higher than 100 ppm/h in LFSA. However, it was indicated that prolonged administration of high concentrations of sevoflurane might lead to significant transient glomerular, proximal and distal tubular injury (9–11). Homocysteine, which is a specific and sensitive marker of renal metabolic function, is an amino acid that is a sulfur-containing metabolite of methionine. In the homocysteine metabolism, there are two major pathways – remethylation back to methionine using vitamin B<sub>2</sub> as a cofactor, and the second pathway is transsulfuration to cysteine using vitamin B<sub>6</sub> as a cofactor. Besides, desflurane causes carbon monoxide poisoning by producing carbon monoxide as enflurane and isoflurane do (8). Carbon monoxide can significantly elevate carboxyhemoglobin concentrations and it is not known if carboxyhemoglobin is degraded to difluorovinyl products, which are nephrotoxic (5, 12). Desflurane and sevoflurane were reported to have no adverse effects on hepatic metabolic function and most of the clinical studies have shown that low-flow anesthesia with desflurane and sevoflurane did not change renal and hepatic functions as well (13–15). Although it was demonstrated that desflurane and sevoflurane might affect renal and hepatic functions in open surgery, to our knowledge, this was not researched in laparoscopic surgery. This study was designed to investigate the effects of sevoflurane and desflurane with low-flow anesthesia (1 L/min) on renal and hepatic functions in patients undergoing laparoscopic abdominal surgery.

## Materials and Methods

### Subjects

Twenty patients with an ASA I-II (the American Society of Anesthesiologists classification) physical score undergoing laparoscopic abdominal surgery were included in this study. Informed consent was obtained from each patient. The study was conducted in accordance with the ethical standards of

the Helsinki Declaration. The demographic characteristics of all subjects, matched for age, height, weight, body mass index (BMI), the duration of anesthesia and surgery, are shown in *Table I*. Patients who had any metabolic, endocrine, hepatic, or renal disease were excluded from the study.

### Methods

Twenty patients were selected randomly to receive sevoflurane (n=10) and desflurane (n=10) by using randomization schemes at a fresh gas flow rate of 1 L/min. Fresh sodalyme® (Dräger Healthcare Products, Inc., Germany) was placed into the canister in both groups immediately before the anesthesia. The patients were premedicated with 0.15 mg/kg intravenous midazolam and 10 µg/kg atropine 30 min before the induction of anesthesia. Anesthesia was induced with propofol (2–2.5 mg/kg), fentanyl (2–3 µg/kg) and rocuronium bromur (0.5 mg/kg) in 100% oxygen. After tracheal intubation, the fresh gas flow rate was set to 4.4 L/min in both groups. After 5 minutes the total fresh gas flow was reduced to 1.0 L/min. The ratio of oxygen to airflow rates was adjusted to maintain the oxygen concentration in the inspiratory limb at 50%. The anesthetic concentration was adjusted to maintain 1.5–2.0% for sevoflurane and 4–6% for desflurane with systolic blood pressure within  $\pm 20\%$  of baseline. An intravenous bolus of 1–2 µg/kg fentanyl and 0.2 mg/kg rocuronium bromur were added in 30 min periods. Ventilation was controlled with a tidal volume of 10 mL/kg and the respiratory rate was adjusted to maintain an end-tidal carbon dioxide (EtCO<sub>2</sub>) value between 35 and 45 mmHg. The anesthetic device used was Datex-Ohmeda ADU® Anesthesia System (Datex-Ohmeda, S/5, Helsinki, Finland). Postoperative antibiotics were restricted to 1 g/d of ceftriaxone up to 3 days after anesthesia.

### Procedures

All patients were monitored by electrocardiography (ECG), for noninvasive blood pressure (BP), peripheral oxygen saturation (SpO<sub>2</sub>) and end-tidal CO<sub>2</sub>. During anesthesia, the end-tidal CO<sub>2</sub> concentration and end-tidal anesthetic concentrations were monitored by mass spectrometry (Datex-Ohmeda, ADU, S/5, Helsinki, Finland). The radial artery was cannulated to permit blood samples to be obtained for serum biochemical analysis before and after anesthesia. Blood samples were obtained before anesthesia and at 24 and 48 hours after the anesthesia for measurement of blood urea nitrogen (BUN), serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), direct bilirubin, total bilirubin and homocysteine levels. All serum urea, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate

dehydrogenase (LDH), gamma glutamyl transferase (GGT), direct bilirubin and total bilirubin analyses were performed by a central commercial laboratory that used an auto analyzer. Creatinine levels and AST, ALT activities were determined on a Hitachi-917 automated analyzer by using commercial kits supplied by Roche Diagnostics (Mannheim, Germany). Homocysteine level was determined by using a commercially available human ELISA kit (Med Systems Diagnostics GmbH, Vienna, Austria) (normal range for adults: 5–15  $\mu\text{m/L}$ ). Creatinine clearance was interpreted by the Cockcroft-Gault formula (estimated creatinine clearance =  $[(140 - \text{age in years}] \times \text{weight in kilograms}] / [72 \times \text{serum creatinine concentration in milligrams per deciliter}]$ ; multiplied by 0.85 for women) (16).

*Statistical analysis*

Data are given as mean values  $\pm$  standard deviation. Intergroup comparisons of the patient characteristics, anesthesia time, operation time, and serum biochemical concentrations were performed using Mann-Whitney U-test and Fisher’s protected least significant difference test. Inter and intragroup comparisons of laboratory data were performed using Friedman and Wilcoxon-rank test repeated measures analysis of variance. A p value < 0.05 was considered statistically significant.

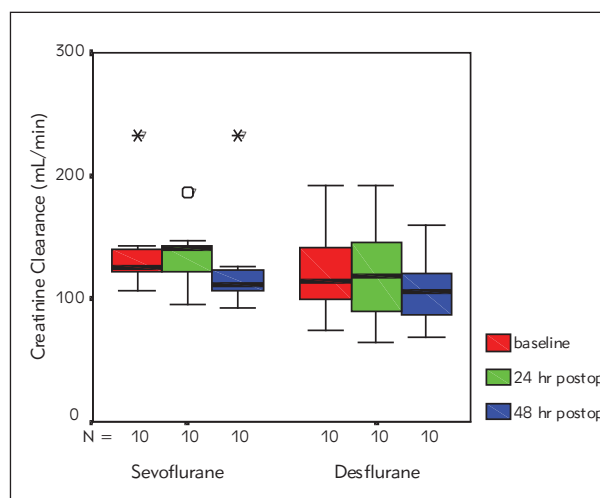
**Results**

Demographic characteristics of the patients studied are listed in *Table I*. There were no significant differences between the two groups with respect to age, weight, BMI, duration of operation and anesthesia time. Renal function parameters such as urea, BUN and creatinine and calculated creatinine clearance did not show significant differences at 24 and 48 hours compared to baseline levels in both groups (*Table II*). Creatinine clearance (Ccr) levels were found to be low at postoperative 24 ( $135.62 \pm 24.95 / 121.33 \pm 40.08$ ) and 48 hours ( $122.35 \pm 40.39 / 104.80 \pm 27.29$ ) compared to the baseline level ( $135.95 \pm 36.03 / 122.11 \pm 35.20$ ) in sevoflurane and desflurane

**Table I** Demographic characteristics of patients.

	Sevoflurane (n=10)	Desflurane (n=10)	P
Age (yr)	43.7 $\pm$ 7.67	47.70 $\pm$ 10.99	Ns
Height (cm)	163.8 $\pm$ 4.10	163.7 $\pm$ 5.86	Ns
Weight (kg)	71.7 $\pm$ 7.30	76.70 $\pm$ 9.48	Ns
BMI	27.2 $\pm$ 3.05	28.95 $\pm$ 3.89	Ns
ASA I/II	7/3	5/5	Ns
Duration of anesthesia	105.5 $\pm$ 18.02	100.50 $\pm$ 18.62	Ns
Duration of surgery	93.0 $\pm$ 17.02	90.50 $\pm$ 17.86	Ns

\*p<0.05 All values are expressed as mean  $\pm$  standard deviation, NS: not significant, BMI: body mass index.



**Figure 1** Serum creatinine clearance (Ccr) levels before and after low-flow anesthesia. The mean (dotted line), median, 25<sup>th</sup>–75<sup>th</sup> percentiles (box boundaries) and 10<sup>th</sup>–90<sup>th</sup> percentiles (whiskers) are shown. Outliers beyond 10%–90% are shown as individual data points. There were no significant differences between the anesthetic groups.

**Table II** Comparison of renal functions between the two groups of patients.

	Sevoflurane (n=10)			Desflurane (n=10)			P
	baseline	24h postop	48h postop	baseline	24h postop	48h postop	
BUN (mmol Urea/L)	11.75 $\pm$ 3.35	12.07 $\pm$ 3.71	12.83 $\pm$ 3.52	11.77 $\pm$ 3.56	11.89 $\pm$ 3.65	12.69 $\pm$ 4.03	ns
Urea (mmol/L)	24.80 $\pm$ 8.09	25.00 $\pm$ 7.18	25.40 $\pm$ 7.91	23.08 $\pm$ 7.03	25.20 $\pm$ 7.08	27.10 $\pm$ 7.09	ns
Cr ( $\mu\text{mol/L}$ )	0.62 $\pm$ 0.11	0.61 $\pm$ 0.07	0.70 $\pm$ 0.14	0.72 $\pm$ 0.19	0.75 $\pm$ 0.26	0.83 $\pm$ 0.20	ns

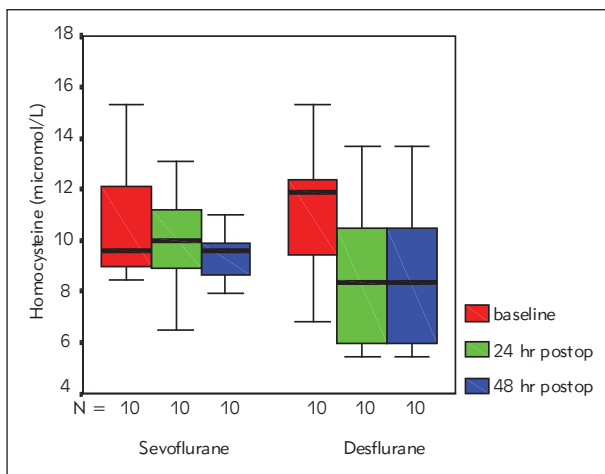
\*p>0.05 All values are expressed as mean  $\pm$  standard deviation, Ns: not significant, BUN: blood urea nitrogen, and Cr: creatinine ( $\mu\text{mol/L}$ ).

**Table III** Comparison of hepatic functions between the two groups of patients.

	Sevoflurane (n=10)			Desflurane (n=10)			P
	baseline	24h postop	48h postop	baseline	24h postop	48h postop	
AST (U/L)	23.00±7.7	24.50±9.2	24.50±9.2	20.80±5.0	24.40±8.8	24.60±6.04	Ns
ALT (U/L)	20.00±7.1	20.70±7.9	22.10±7.3	21.20±9.0	22.20±11.4	25.90±11.3	Ns
GGT (U/L)	13.40±3.3	12.90±3.6	13.50±2.8	18.10±6.1	18.60±7.74	18.90±7.2	Ns
LDH (U/L)	357.40±63.3	341.20±82.7	353.50±71.7	346.70±28.9	342.30±20.1	357.20±20.9	Ns
Dr. bil (μmol/L)	0.15±0.07	0.17±0.08	0.16±0.09	0.14±0.05	0.14±0.05	0.15±0.07	Ns
T. bil (μmol/L)	1.01±1.4	0.61±0.2	1.06±1.7	0.50±0.09	0.47±0.08	0.52±0.07	Ns

\* $p > 0.05$ . All values are expressed as mean  $\pm$  standard deviation; NS: not significant.

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, Dr. bil: direct bilirubin, T. bil: total bilirubin.



**Figure 2** Serum homocysteine concentrations before anesthesia and after low-flow anesthesia. The mean (dotted line), median, 25<sup>th</sup>–75<sup>th</sup> percentiles (box boundaries) and 10<sup>th</sup>–90<sup>th</sup> percentiles (whiskers) are shown. Outliers beyond 10%–90% are shown as individual data points. There were no significant differences between the anesthetic groups.

groups, respectively. These differences were not significant (*Figure 1*). Homocysteine levels which showed renal metabolic function did not change significantly at 24 ( $10.00 \pm 1.82 / 8.51 \pm 2.7$ ) and 48 hours ( $9.44 \pm 0.96 / 8.51 \pm 2.7$ ) compared to baseline ( $10.58 \pm 2.23 / 11.02 \pm 2.2$ ) levels in both the sevoflurane and desflurane groups (*Figure 2*). Hepatic effects of low-flow anesthesia were tested by serum AST, ALT, GGT, LDH, direct bilirubin and total bilirubin concentrations. There were no significant differences between the two groups from baseline to 24 and 48 hours. There was no increase in the postoperative levels of hepatic function parameters in either of the anesthetic groups (*Table III*).

Differences between the preoperative and postoperative values (delta values) of biochemical parameters were similar for both anesthetic groups ( $p > 0.05$ ).

## Discussion

To our knowledge, anesthesia techniques and surgery are important for changing the biochemical parameters. It was shown that surgery and anesthetic agents produced cellular oxidative toxic metabolites which damaged cellular function and tissue structure (17). It is preferred to cause minimal reactive oxygen species by using volatile anesthetic agents in low flow anesthesia (18). Especially in low flow anesthesia reactive oxygen species (ROS) are reduced due to the consumption of minimal sevoflurane and desflurane (19). Therefore, in low-flow anesthesia and laparoscopic surgery morbidity and mortality are reduced (1, 20).

Volatile anesthetics such as sevoflurane or desflurane produce oxidative toxic effects. Plasma ROS products are more decreased after the administration of sevoflurane than after desflurane, providing beneficial effects on the cellular metabolism now that biochemical oxidative products are decreased (2, 21). In our studies, we aimed to show the advantages of low-flow anesthesia with both sevoflurane and desflurane in laparoscopic surgery. Low-flow anesthesia (1–1.5 L/min) reduces the inhalation anesthetics consumption by nearly 40%–75%, compared to the circle system under high-flow anesthesia (2–6 liter/min). In addition, carbon dioxide (CO<sub>2</sub>) absorbents, which have been used in anesthesia rebreathing circuits, reduce the consumption of inhalation anesthetics (3, 22). The new anesthetics desflurane and sevoflurane, which are licensed for use in humans, offer theoretical and practical advantages over other volatile anesthetics. Sevoflurane has several properties which make it potentially useful as a maintenance anesthesia (23). The lower solubility of both agents provides improved control of delivery and faster rates of recovery compared with izoflurane or enflurane (24). Desflurane can cause airway irritation and sympathetic stimulation in humans. It causes a decrease in erythrocyte volume, which recovers after four days, and increases the



leukocyte count and blood glucose level (25, 26). Armbruster et al. reported that desflurane caused a dose-dependent decrease in hepatic arterial blood flow in a pig model. However, it did not change hepatic metabolic functions significantly, although O<sub>2</sub> delivery to the whole body and the liver was markedly reduced at high concentrations over 8.3% (13). Suttner et al. (14) showed that hepatic function was well preserved in elderly patients anesthetized with desflurane or sevoflurane. On the contrary, metabolites of sevoflurane and breakdown products from its reaction with carbon dioxide absorbents theoretically can result in hepatic and renal damage. Nephrotoxicity of sevoflurane comes from direct alkylation of CpA, but such toxicity has not occurred despite extensive medical use (24, 27). Although there are some differences between these two anesthetic agents, we found that sevoflurane and desflurane did not alter the hepatic enzyme levels. Although BUN and serum creatinine are the most commonly used indicators of injury in the studies of sevoflurane nephrotoxicity, they have not revealed renal injury. Especially, creatinine clearance and the homocysteine level, which has been recently accepted as a marker of renal metabolic function, are used in renal toxicity (28). Increased plasma tHcy concentrations are found with methionine-rich diets, low vitamin B intake, male gender, increasing age, impaired renal function, and genetically determined defects of the enzymes involved in homocysteine metabolism. This is in good agreement with the findings of other investigations: Litz et al. (29) showed that general anesthesia with desflurane did not aggravate renal impairment in patients with preexisting renal insufficiency. Several studies have shown that sevoflurane anesthesia in open surgery at various fresh gas rates (1–4.4 L/min) was found to be safe in patients with normal renal function (15, 30). To our knowledge, sevoflurane anesthesia can cause transient dysfunction of several parts of the human nephron. Albuminuria and slightly greater proteinuria indicate glomerular injury (6). Therefore, it has been suggested that low-flow sevoflurane anesthesia (<1 L/min) would not be safe in patients with renal impairment (4). Patients with preexisting renal disease are at an increased risk for further postoperative deterioration of function and CpA nephrotoxicity may add to this risk. Eger et al. found that renal injury, as defined by postoperative concentrating defects and increased urinary levels of N-acetyl-b-glucosaminidase, correlated with increased inorganic fluoride levels produced by sevoflurane biodegradation (6). Although CpA was shown to exhibit nephrotoxicity in rodents, no significant changes in renal function parameters were reported in surgical patients (5, 26, 31, 32). In a previous study, it was reported that plasma inorganic fluoride concentrations were regularly increased after sevoflurane anesthesia and were not associated with nephrotoxicity.

Histological examination in horses revealed that sevoflurane anesthesia was associated with mild microscopic changes in the kidney involving mainly the distal tubule, but no remarkable alterations in hepatic tissue. These results indicate that horses can be maintained in a systemically healthy state during unusually prolonged sevoflurane anesthesia with minimal risk of hepatocellular damage from this anesthetic (12, 26). In human studies, sevoflurane and desflurane were found to have no adverse hepatic effects (33). It was also suggested that desflurane was a safe agent even in patients with chronic hepatic and renal diseases (34). In our study, we also did not find any deterioration in hepatic functions. It was shown that pneumoperitoneum of 10 mmHg, resulting from the laparoscopic surgery technique, caused a 70% decrease in GFR (32). It was also suggested that the pneumoperitoneum reduced the hepatic portal blood flow, although it did not alter the clinically important postoperative hepatic transaminases (35–37). In these patients, selection of the anesthetic agent, which has minimal or no effect on renal and hepatic functions, and a low fresh gas flow rate are very important. CO<sub>2</sub> insufflated during the pneumoperitoneum period is absorbed into circulation, which may cause many side effects. During low-flow anesthesia reduced CO<sub>2</sub> is produced due to lower metabolism of the anesthetic agent. Thus, low-flow anesthesia may minimize the total amount of CO<sub>2</sub> in the pneumoperitoneum by reducing gas consumption resulting from anesthetic agent metabolism (3–37).

In conclusion, we demonstrated that low-flow sevoflurane and desflurane anesthesia did not impair renal and hepatic functions. Sevoflurane has more protective effects than desflurane that result in decreased morbidity and mortality. The present data show for the first time that the choice of low flow anesthesia with volatile anesthetics is associated with a better outcome after laparoscopic surgery. In addition, low flow anesthesia did not affect the biochemical parameters and may be a good alternative to the conventional high-flow anesthesia techniques. We showed that creatinine clearance and homocysteine are important diagnostic biomarkers for renal metabolic function. Further studies are required to assess in terms of biochemical parameters or new diagnostic markers the other potential advantages of low-flow techniques, with particular regard to economic considerations.

*Acknowledgements.* This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### **Conflict of interest statement**

The authors stated that there are no conflicts of interest regarding the publication of this article.

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*Received: April 20, 2011*

*Accepted: May 19, 2011*